Snake Venom in Anticancer Drug Development: Potential Targets and Current Perspectives

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ABSTRACT
Many animals active secretions have been used to create novel medications to treat ailments such as hypertension and cancer. Snake venom toxins have made major contributions to treating various medical disorders. There have been several research studies that have been published characterizing and clarifying snake venom's anti-cancer potential. Cancer treatment is one of the primary applications for protein peptides and enzymes derived from various animal species. When separated, several of these proteins, peptides, and enzymes from snake venom and assessed may bind selectively to cancer cell membranes, influencing migration and invasion. These cells proliferation Some of the chemicals discovered in snake venom have a high potential. Cystatin-rich snake venom influences tumor invasion and metastasis. A non-cholinesterase Arginine ester hydrolase enzyme in snake venom reported to have increased sensitivity to chemotherapy and radiotherapy in animal models. Snake thrombin-like enzymes, are serine proteases found in snake venom that causes haemostasis and hypofibrinogenemia. Cancer-associated fibroblasts was reported to have role in quiescence and also prevents cancer cell migration, in addition to downregulating the epithelial-mesenchymal transitioning. Collagen Tumor-associated hyaluronic acid (HA) and hyaluronidase (HAase) was crucial for tumor growth and metastasis promotion. Phospholipases are enzymes that break down phospholipids, which are key components of cell membranes are involved in cancer cell migration, invasion and metastasis. AMP-activated protein kinase (AMPK), a metabolic protein plays a crucial role in energy regulation and cell survival and studies reported its role in tumour suppression. The components of snake venom and its potential as a cancer-fighting agent, we summarised the key findings in this review.

1. Introduction

Snake venom is the secretion of poisonous snakes that are created and stored in specific parts of their bodies known as venom glands. The majority of the venoms are complicated. a combination of proteins, peptides, enzymes, and other substances non-protein inclusions, and toxins[1]. Although most are safe, some can be hazardous to some extent. Globally snake venom is a major cause of death and morbidity. Snake venom affects the human body differently based on its intensity and kind. Distinct species have different venom forms, varying according to the species, geographical region, and other factors. Its environment, climate, age, and so forth (Table 1)[1]. Snake venom is non-lethal whether consumed in liquid or crystal form. It will be expelled intact after drying through the mouth. It includes anticoagulant proteins. It simply causes toxicity when comes in touch with blood. There are three categories of snake venom depending on their effects. Hemotoxic venoms affect the cardiovascular system, Cytotoxic venoms target particular blood cell activities, and the neurological system of the human body is harmed by neurotoxic venoms, locations, or muscles. The two primary purposes of snake venom are to paralyze the victim and initiate the digesting process. Blood clotting and tissue necrosis are caused by the hydrolysis of proteins and membrane components by the enzymes found in snake venom. Attacks on neuro-muscular connections, nerve membranes, and branches that result in paralysis are caused by venom components. There are several classifications for snake venom based on how it works. Certain venomous substances bind to Cholinergic receptors and function biologically without inducing any action. When a prey's respiratory muscles give out, it usually dies. A group of poisons either prevents or is just responsible for skin and connective tissue damage[2]. The cardiotoxins in the venom induce cell damage membrane or interfere with drug transport or the transmission of signals across the membrane. Secreted phospholipases A2 (sPLA2) isolated from Cerastes and Macrovipera lebetina have promising antitumor and antiangiogenic properties since they act specifically on integrins α5β1 and ααβ. In human skin melanoma cells, sPLA2 from Daboia russelii siamensis venom is cytotoxic and inhibits cell migration. It also lowers B16F10 tumor lung colonization. Melanoma cells

were found in BALB/c mice. Anticoagulant effects of sPLA2. This may help avoid recurrent thrombosis, the second most common cause of death. Cancer is a leading cause of mortality among patients. Nanoparticles tagged with snake venom components have been shown to act preferentially on tumor cells while not affecting normal cells[2].

2. Snake Venom Components:

Cystatin-rich snake venom reduces tumor invasion and metastasis. By mixing snake venom components with nanoparticles, cancer cells can be targeted specifically[3]. An essential ingredient in the creation of immunoconjugates, which are more targeted against cancer cells, is the cobra venom factor[4]. The enzyme LAAOs derived from snake venoms induce apoptosis, changes in cell cycle processes, and cytotoxicity, and they have promising potential for creating new anticancer therapies. Some of the potential processes underlying the activities of snake venom LAAOs include the production of hydrogen peroxide during enzymatic reactions, caspase activation, and contact with membrane receptors[5]. The components of snake venom encourage cell death and prevent cell multiplication. The following are some of the mechanisms of action: increasing calcium ion influx, causing cytochrome C release, altering the expression of proteins that regulate the cell cycle, damaging cell membranes, inhibiting nucleic acid synthesis to suppress cell proliferation, inhibiting platelet action to prevent fibrin formation, preventing thrombin-induced metastasis, inducing cancer cell apoptosis to control tumor size. When compared to normal cells, tumor cells are significantly more affected by changes in cellular metabolism as a result of snake venom cytotoxicity[6].

Table 1: Species of some medicinally important snakes found in India.

S. no.	Family	Scientific names	Common names
1.	Viperids	Vipera russelli	Saw scaled viper
2.	Elapids	Naja naja	Indian cobra
3.	Elapids	Naja oxiana	Central Asian Cobra
4.	Elapids	Ophiophagus	Hannah-king cobra
5.	Viperids	Echis carinatus	Russell's viper

2.1 Proteolytic enzymes

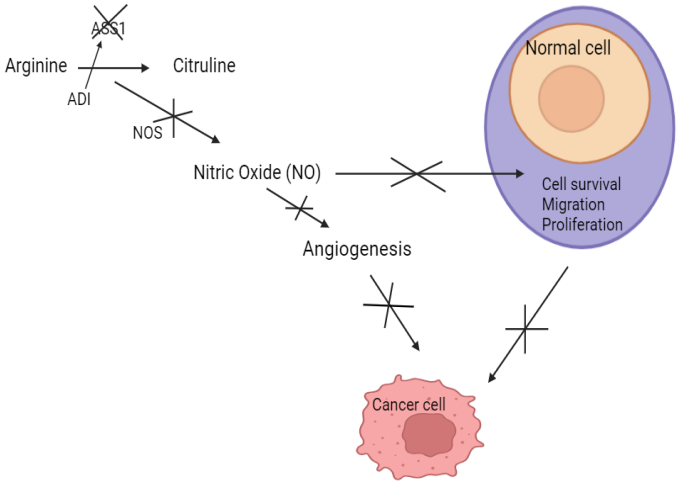
These include catalysis which is also aided by some metal ions. They are integral in the actions of venom proteases. Proteolytic enzymes specifically act as special proteins which facilitate breaking down of other proteins into very small parts, eventually breaking it into amino acids. The proteolytic enzymes can feature greatly in digestion processes, angiogenesis, invasion, and even metastasis. They consist of all enzymes that help break tissue proteins and peptides, and have molecular weights of 20000-95000 Da[7]. They appear in many living organisms like bacteria and plants but mainly are found in animals. The two general categories of proteolytic enzymes are exopeptidases and endopeptidases. Their types include some others: aspartic acid-, cysteine-, glutamic acid-, metallo-, serine-, and threonine-dependent proteolytic enzymes[8]. Oligopeptides are those enzymes that have the specialty to attack shorter chains of peptides. Growth factors in sprouting angiogenesis activate receptors on endothelial cells. This results in the release of proteases that degrade the basement membrane. This enables endothelial cells to migrate and to form new sprouts that anastomose with other vessels. Degradation is also part of normal and aberrant angiogenesis. The degradome includes proteases that degrade surrounding tissue as cancer invasion and metastasis occur. Initially, it was thought that invasion and metastasis occurred later in the cancer development process. However, studies have established that these processes are reliant upon protease activity even during the early stages of cancer[9].

2.2 Arginine ester hydrolase

This is one among the non-cholinesterase enzyme discovered in snake venom. Which make the peptide linkage to hydrolyse that is also been reported in crotalid, viperid but not found in elapid venoms[10]. Certain enzymes, such BAEE and TAME, that hydrolyse arginine ester were isolated from the mamushi venom[11]. Arginine ester was hydrolysed by the AE hydrolase in venom, while lysine ester and arginine amide were not Less than 10% of the AE hydrolytic activity of crude venom was present in the bradykinin-releasing enzyme. The clotting enzyme or AE, had the same hydrolytic activity as fibrinogen. The protein enzyme accounts for 45% of the total AE hydrolytic activity in the venom[12]. Nitric acid synthase is an enzyme that converts l-arginine into nitric oxide (NO). In blood vessels, NO produced by endothelial cells helps maintain vasodilation. The l-arginine: Nitric oxide pathway activates soluble guanylate cyclase in tissues, with NO acting as a natural stimulant. While NO is effective against cancer, its clinical use is limited due to the risk of low blood pressure from systemic

treatments[13]. Research shows that NO can enhance the effectiveness of traditional cancer therapies. For example, increasing iNOS levels can speed up radiation-induced cell death in colorectal cancer, and NO delivery agents can make tumor cells more sensitive to cisplatin in animal models[14]. However, many tumors develop or have natural resistance to chemotherapy, sparking interest in identifying biological markers for treatment success and creating new methods to reduce chemoresistance[15].

Figure 1: Illustration of NO production through nitric oxide (NO) synthase (NOS)-catalyzed conversion from arginine, which is inhibited Many cancer cell migration signaling pathways do this, as well as those leading to normal functions of cells including survival and proliferation and the progression of a cancer cell in angiogenesis. ASS1 is inhibited leading to the conversion of arginine into citrulline while ADI causes breakdown of arginine.



2.3 Thrombin and Thrombin like enzyme

Snake thrombin-like enzymes, SVTLE are serine proteases in snake venom that cleave fibrinogen, an essential blood-clotting protein, causing hemostasis and hypofibrinogenemia. Unlike thrombin, SVTLEs do not degrade the Aα and Bβ chains of fibrinogen nor activate some clotting factors. They make up 10–24% of snake venom and are also found in spider, bee venom, as well as other specific plants. SVTLEs can cause blood clotting, thrombosis, neurological disorders, and stimulate the growth of new blood vessels that cause angiogenesis. These compounds clinically have been used to reverse conditions of ischemia, thrombosis, heart attack, and even able to dissolve kidney stones. Some inhibitors include carbon monoxide, suramin, and Jatropha leaf extract that can affect their ability. SVTLEs are usually monomeric with molecular weights ranging from 26–67 kDa and are often glycosylated. Though the role that these play is not specifically known, their contribution is of importance in clotting processes in blood[16].

Tissue factor (TF) triggers a hypercoagulable condition in advanced cancer that results in thrombin generation to promote metastasis by promoting the deposition of fibrin and platelets and signaling through the thrombin-activated receptor PAR1. While thrombin does not activate PAR2, it enhances the effect mediated by thrombin on metastatic cells by interacting with PAR1. Beyond promoting metastasis, TF contributes to the growth of tumors by inducing angiogenesis[17].

2.4 COLLAGENS

Collagen is the most abundant protein in the body, forming fibres that create connective tissue. It provides strength and flexibility to tissues, making them resistant to stretching. The right-handed helical glycoprotein collagen consists of three left-handed helical α chains, which may be the same or different. The amino acid sequence of these α chains is typically a repeat of the glycine–X–Y sequence, where X and Y are often proline or hydroxyproline—hydroxyproline being essential for the thermal stability of collagen. In the presence of calcium near the endoplasmic reticulum, heat shock protein 47 and protein disulphide isomerase assist the enzymes procollagen N-proteinase and C-proteinase in converting procollagen to collagen. Enzymes like endopeptidases and metalloproteinases can also cleave procollagen, with the removed propeptides helping to regulate collagen production. Chlorine takes part in covalent cross-linking through glycosylation, through

transglutaminase, and through LOX (lysyl oxidase) in both intermolecular and intramolecular linkages of the protein. In the extracellular matrix, different types of collagen are broken down by matrix metalloproteinases (MMPs), which are zinc-dependent enzymes that degrade collagen[18].

2.4.1 Targeted therapy- collagen

Cancer-resistant people have challenges when getting the necessary treatment for malignancies mainly caused by cancers. The first step for treating a cancer would be specifically attacking the cancer cells and the tumor microenvironment, which collagen is being proposed. Although one may want to see collagen as the perfect target, the picture is slightly different since the genetic stability of collagen is also a consideration. It is collagen's solid genetic structure that has been the hallmark of this molecule. It still holds good quality material after all these years [19]. The molecule is unchanged in its 3-dimensional organization in the process. Because collagen is involved in such a large number of different cancer types, the potential therapeutic benefit of modifying the state of this protein in invasive cancers to an earlier, non-invasive state provides exciting avenues for new research [20]. The modulation of collagen involves the inhibition of several biosynthetic processes and the distribution patterns of certain inhibitors targeted specifically toward the collagen biosynthesis enzymes [18]. Signalling pathways in cancer cells are modified by either randomized components of the extracellular matrix (ECM) or through the direct exposure of cells to a variety of classes of collagenases, potentially tailored to induce or reverse alterations in collagen expression. While numerous inhibitors were discovered, very few were evaluated in cellular and animal models. Furthermore, intrinsic interaction complexes within the protein studied, compromise these indirect methods, impacting collagen processing by numerous molecular mechanisms and signalling cascades[21]. Most relevant to the current study is the role of cancer-associated fibroblasts, CAFs. The quiescent and myofibroblast phenotypes were used to define the CAFs, whereas the presence of lipid droplets that store vitamin A in the cytoplasm is a signature for the identification of cachectic CAFs which loses these granules along with an increase in the expression of α-SMA after their activation. On the other hand, a vitamin A derivative called all-trans retinoic acid (ATRA) has been demonstrated to send both CAFs and CSLCs into quiescence and also prevents cancer cell migration, in addition to downregulating the expressions associated with epithelial-mesenchymal transitioning; however, clinical trials have only just recently begun recruiting. Some studies, but again of the contact between cancer cells and the collagen matrix that shows that the latter morphed towards cancer to better manage the former in those situations [22].

Rather than acting through a pathway of direct effect on insulin secretion and with CYP24A1 expression correlated with poor prognosis, low CYP24A1 activity can have direct anti-proliferative effects on transformed ductal cells and activate autocrine vitamin D signaling in multiple cellular compartments as the course of PDAC progression. Despite this, a phase III clinical trial is currently underway to assess if there is any benefit to high-dose vitamin D3 treatment in the results of patients who undergo pancreatic cancer surgery. Additionally, the vitamin D receptor ligand calcipotriol has been shown to effectively regulate CAFs and cause them to become inactive. Paricalcitol was selected for the continuing clinical trials to target the therapy of pancreatic ductal adenocarcinoma (PDAC). It is important to note that here we have an example where MMP activity may be either pro- or anti-cancer exerting its effects across several different pathways controlling the same pathophysiological process. With regard to preclinical studies, the combination of an anti-MMP-9 antibody with standard cytotoxic therapy based on nab-paclitaxel decreased collagen type I and metastatic burden significantly more than nab-paclitaxel alone in PDAC mouse models. Therapies that target cancer by using treatments destined for collagen may make differential effects concerning delivery therapeutics and treatment outcome in tumor therapy for one disease [23]. Like monotherapy with collagenase, side effects could be considerable and balance expected therapeutic outcome. overall survival rates were not significantly improved in patients with metastatic pancreatic cancer when the sonic hedgehog antagonist vismodegib was incorporated into a phase Ib/II trial alongside gemcitabine. Therefore, this indicates that future treatment strategies focusing on the use of collagen inhibitors with standard cancer chemotherapy and radiation protocols may be developed[24]. Delivery of collagenase with trastuzumab via thermosensitive hydrogels showed anticancer potential in vivo. There are rare clinical studies and most of the studies target on signaling pathways or receptors. Limited and controversial anti-collagen evidence reveals the complicacy of collagen functions. Although it is required for the tissue structure of normal tissues, it plays a crucial role in tumorigenesis and subsequent clinical outcomes. The collagen reduces by activating persisting cancer cells that are left behind, and it is involved in the structure of an abnormal ECM with microvascular structures. In particular, collagen may inhibit carcinogenesis during initial stages but promote progression of carcinoma cells at later stage variants. Additionally, the degradation product of collagen can persist to advance further angiogenesis and invasion by the carcinoma. Cancer-associated fibroblasts (CAFs)

are cells that produce mainly stromal collagen and may have antitumor or protumor functions. Apart from stabilizing the vasculature, epithelial and endothelial cells that produce basement membrane collagen allow cancer angiogenesis (a little easier to understand), thus allowing structured tissues to enter the bloodstream[25]. In addition, heterogeneity between patients as well as patient-to-patient variation both in genetics as well as epigenetic profiles could be the cause for activity or failure of some anticancer agents in clinical trials. Thus, the efficacy of collagen to content, crosslinking and alignment in homogeneous applications can be crucial contribution for its utilization as a therapeutic target on cancer. It can also work as a drug carrier, or at sites of targeting therapeutic agents[26]. Hybrid carriers with collagen and cell penetrative peptides that presented enhanced resistance to enzymatic degradation were also demonstrated. Injections of the oncolytic vaccine - a recombinant adenovirus with a gene for the collagen-type binding domain fused to a single-chain fragment from cetuximab-have already demonstrated preliminary success at least[27]. This novel approach has led to the total elimination of tumors in a model with substantial safety and efficacy. In that sense, the importance of immunoconjugate therapy using the cancer-collagen-targeting method has thus been explained and can be potentially valued for application in oncology treatment. This innovative approach opens new avenues for researchers and clinicians as they continue to strive to fight cancer more effectively with reduced side effects[28].

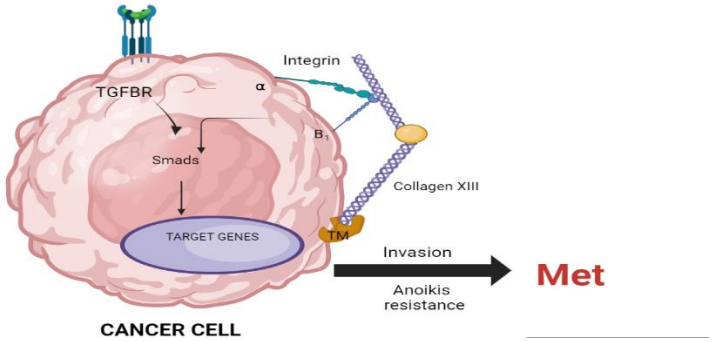


Figure:2: The figure depicts the role of TGFBR signaling and integrin-collagen XIII interactions in cancer cell invasion and anoikis resistance. These pathways promote cancer metastasis (Met) by regulating target gene expression through Smad proteins and reinforcing cell-ECM adhesion, driving invasive behavior and survival.

2.5 HYALURONIDASE

A system including tumor-associated hyaluronic acid (HA) and hyaluronidase (HAase) has been defined as critical for tumor growth and metastasis promotion. The bulk of this HA is synthesized in situ within tumors by HA synthases, although a quantitatively more significant source is the serum and plasma of cancer patients; it acts on cells by binding to receptors CD44 and RHAMM. Binding of HA to these receptors initiates signals that favor growth and proliferation of the tumor, metastasis, angiogenesis, movement of tumor-associated macrophages, and chemotherapy resistance. Recent studies show that 4-methylumbelliferone (4-MU), an inhibitor of HA synthesis, has been proven to exert antitumor effects in prostate cancer. However, another essential element of this machinery is HYAL-1, hyaluronidase that is released by cancer cells. HYAL-1 has been demonstrated to support cancer growth, invasion, and angiogenesis in models of prostate and bladder cancers and also as a biomarker for predicting metastasis[29]. Although it is an essential enzyme involved in the process of cancer progression, treatments targeting HYAL-1 have not yet been developed. More importantly, although small HA polymers (sHA) alter cell functions like proliferation and movement, they remain understudied for therapeutic purposes. HA synthases, the enzymes that synthesize the HA, also have not been exploited as drugs, but antisense oligonucleotides have shown that HAS1 suppression can massively stop the proliferation of bladder cancer cells and halt the progression of prostate cancer cell cycle[30].

The invasiveness and migratory ability of bladder cancer cells has significantly been attenuated by a reduction in HAS1, resulting in more than five-fold inhibition of tumor growth and angiogenesis. Furthermore, there is evidence of feed-forward loop between HA synthesis and HA receptor expression, with knockdown of HAS1 resulting in a decrease in CD44 transcription[31]. High levels of HAS1 in bladder, prostate, and kidney carcinomas have been associated clinically with HA presence in the tumors and thus predict poor prognosis, which further supports its involvement in tumor progression. Reduction of HAS2 and HAS3 expression also reduces growth and metastasis of breast and osteosarcoma tumors. Radiation-induced DNA damage and

apoptosis have also been found to be increased in cancer cells following HAS2 knockdown. HAS2 and HAS3 levels have been correlated with chemotherapy resistance and with an increased risk of anthracycline treatment-related heart disease. Cancer cells often express more than one HA synthase; it may be more effective in inhibiting overall HA synthesis by targeting small-molecule inhibitors than by inhibiting individual synthases[32].

2.6 Phospholipase

Phospholipases are enzymes that break down phospholipids, which are key components of cell membranes. These enzymes are classified into two main groups: acyl hydrolases, which include phospholipase A1 (PLA1), phospholipase A2 (PLA2), phospholipase B (PLB), and lysophospholipase (LysoPLA1/2), and phosphodiesterases, which include phospholipase C (PLC) and phospholipase D (PLD). Found in nearly all cells, phospholipases exist in secreted, membrane-bound, or cytoplasmic forms, and their activity often depends on the presence of cofactors[33]. Their functions are diverse and include digestive roles, such as breaking down phospholipids in snake and wasp venom, maintaining and remodeling cell membranes by altering fatty acid chains, and regulating cell signaling by producing lipid molecules that help with communication between cells. Of these, PLA2, PLC, and PLD are particularly well-studied for their roles in generating bioactive lipids. This review will focus on PLA1 while briefly discussing other phospholipases and their biological significance for a broader understanding[34].

2.6.1 Phospholipase A1 (PLA1)

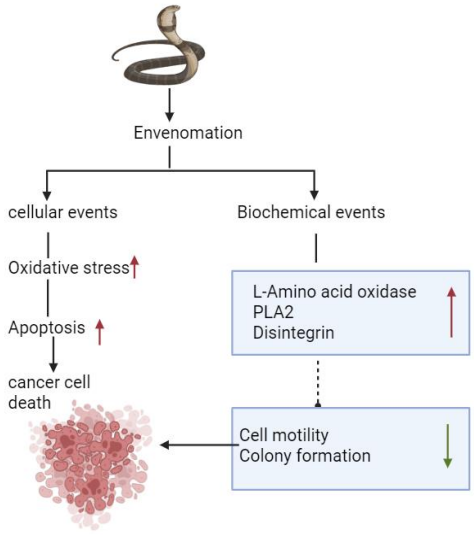
Phospholipase A1 is an enzyme that specifically hydrolyzes fatty acids at the SN-1 position of phospholipids. The reaction products of PLA1 include a free fatty acid and a lysophospholipid. This particular class of phospholipase remains poorly characterized, with no available crystal structures for any authentic PLA1. The functional roles of PLA1 in various organisms have not been conclusively determined. Traditionally, the biological significance of this acyl hydrolase has been associated with its expected involvement in the Lands Cycle, a process of deacylation and reacylation that phospholipids are believed to undergo to maintain a balanced composition of molecular species in membrane bilayers. However, only one PLA1 has been directly linked to the Lands Cycle, while the cycle itself has been consistently demonstrated at the sn-2 position through the action of phospholipase A2, with ongoing research further investigating this phenomenon. Although it is conceivable that PLA1 may have a similar function, such a conclusion cannot be drawn from current experimental evidence[35]

2.6.2 Phospholipase A2

Phospholipase A2 (PLA2) is an enzyme responsible for the hydrolysis of glycerophospholipids at the sn-2 position, resulting in the formation of fatty acids, typically unsaturated, and lysophospholipids[36].

1.6.2(a) $sPLA_2$ and cancer: sPLA2-IIA is one of the secreted phospholipase A2 variants with multiple functions in cancer and whose activity is usually tissue-type dependent. This endogenous enzyme has been implicated in tumor development. Research identified some mouse strains that lack this gene due to mutation are susceptible to colorectal tumors. On the contrary, transplantation of these mice into which the Pla2g2a gene has been added brings about a significant decrease in tumour formation, suggesting sPLA2-IIA may serve as an anti-tumour agent in colorectal cancers. Human studies also show that higher levels of sPLA2-IIA levels in gastric adenocarcinoma have been associated with increased survival rates and lesser metastasis, thus indicating it is protective against GI cancers. However, sPLA2-IIA may aid in the development of the tumor in other organs. For example, it can show if the tumor is aggressive in prostate cancer. In mice with skin-specific Pla2g2a genes, it increases the risk of getting skin cancer from chemicals[37]. Another type, sPLA2-III, is found in the cells that line blood vessels and in tumor cells in different human cancers. Studies have demonstrated that mice with colorectal cancer cells expressing sPLA2-III produce bigger tumors than those without sPLA2-III. Thus, sPLA2-III seems to support tumor development. In addition, sPLA2-III is a potential biomarker for colon cancer in humans, since specific alterations of the PLA2G3 gene are associated with increased risks of colorectal cancer[38].

Figure 3: Snake envenomation has been demonstrated to cause oxidative damage and manipulation of programmed cell death leading to the death of cancer cells. Several biochemical elements such as L-amino acid oxidase, PLA2 and disintegrin suppress cell motility and formation of colonies which improve this effect.



2.6.3 PHOSPHOLIPASES B &C

Phospholipases B refers to a class of enzymes known as lysophospholipases, which facilitate the hydrolysis of monoacyl phosphatides, resulting in the release of free fatty acids and the production of glycerophosphoryl derivatives [39]. Phospholipase C (PLC) is an essential enzyme in cellular signaling, responsible for hydrolyzing a specific membrane lipid known as phosphatidylinositol bisphosphate (PIP2) into two key signaling molecules: inositol triphosphate (IP3) and diacylglycerol (DAG). The production of IP3 initiates the release of calcium ions from intracellular stores, resulting in elevated calcium levels within the cell, which are vital for various functions such as secretion, cellular growth, and muscle contraction. Concurrently, DAG activates protein kinase C (PKC), a critical protein that modulates numerous cellular activities, including growth and differentiation[40]. The signaling pathway involving PLC-γ1 is particularly important as it can promote cell growth and proliferation. Notably, heightened levels of PLC-γ1 have been detected in certain types of cancer, including breast cancer, indicating that this enzyme may play a role in cancer progression. While the precise mechanisms through which PLC-γ1 affects tumor growth remain unclear, its overexpression has been associated with enhanced signaling pathways that facilitate the proliferation of cancerous cells[41].

2.6.4(a) PLCε: A Crucial Yet Contentious Role in Carcinogenesis

There is substantial evidence indicating that alterations in the metabolome, influenced by factors such as inflammation, hypoxia, nutrient deficiencies, and cancer therapies like chemotherapy or radiotherapy can contribute to the development of various diseases, including cancer. A hallmark of cancer is metabolic reprogramming, wherein cancer cells modify their metabolic processes to fulfill the heightened energy and biosynthetic requirements necessary for survival and proliferation in adverse conditions. Rapidly proliferating tumors frequently exhibit significant alterations in lipid metabolism, characterized by increased fat synthesis (de novo lipogenesis), which not only supplies additional energy but also generates molecules such as diacylglycerol and cholesterol. These molecules can activate signaling pathways that are crucial for cancer progression, metastasis, and therapeutic resistance. PLCε, the largest enzyme in the phospholipase C family, possesses distinctive properties that enable its involvement in various signaling pathways, thereby influencing different tumor types. PLCε can be activated by epidermal growth factor (EGF), G-protein-coupled receptors (GPCRs), and the Rho signaling pathway. In addition to its conventional function of hydrolyzing phospholipids, PLCε is capable of interacting with Ras family GTPases, thereby affecting pathways associated with cell growth and survival. Research has indicated that the positioning of PLCε within a cell can shift based on upstream activators like H-Ras or Rap1A, underscoring the context-sensitive nature of PLCε's role in cancer cells. In a similar vein, AMP-activated protein kinase (AMPK), another metabolic protein that plays a crucial role in energy regulation and cell survival during stress, can suppress tumor growth when excessively activated, further demonstrating the variable roles of metabolic proteins in cancer depending on the surrounding context[42]

3. Conclusion

Snake venom has a complex mixture of proteins peptides and various compounds. Snake venom prevents cell proliferation, and autophagy, prevents micrometastais, and increases cell death by various pathways as we

discussed in this review. Snake venom components showed a good potential for cancer drug development. Preclinical studies have reported the anticancer properties of venoms. The potential target identification of anticancer potential of various components of snake venom looks promising and currently various drugs developed from snake venom components are in different phases of drug development.

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